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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,464	10/18/2001	William D. Huse	AME-06381	7635

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,464	HUSE ET AL	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,12-16,18-22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,12-16,18-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

1. The request filed on 4/1/04 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/982464 is acceptable and a RCE has been established. Claims 1-4, 6-10, 12-16, 18-22 and 24 are pending and are currently under prosecution. An action on the RCE follows.

2. Claims 1, 7, 13, 19 have been amended and claims 5, 11, 17, and 23 have been cancelled.

3. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.

4. The following Office Action contains a NEW GROUND of rejection.

Rejections Withdrawn

5. The rejection of claims 1, 3-7, 9-13, 15-19, 21-24 under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (U.S. Patent 6,312,693, filed 2/1999) is withdrawn in view of the 1.132 Declaration filed.

6. The rejection of Claims 1-24 rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter is withdrawn in view of the arguments presented and the 1.132 declaration.

7. The rejection of claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over Aruffo et al (U.S. Patent 6,312,693, filed 2/99) as applied to claims 1, 3-7, 9-13, 15-19, 21-24 above, and further in view of Hagiwara et al (U.S. Patent 5,589,573, issued 12/96) is withdrawn in view of the 1.132 Declaration filed.

Response to Arguments

8. The rejection of claims 1-4, 6-10, 12-16, 18-22 and 24 under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Nature 321:522, 1986) and further in view of Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and Soderlind et al (Gene 160:269-72, 1995) and Hagiwara et al (U.S. Patent 5,589,573, issued 12/96) is maintained.

The response filed 4/1/04 has been carefully considured but is deemed not to be persuasive. The response seems to argue that the references of Yelton and Soderlind are non analogous art because they do not discuss modifications in the context of donor/acceptor (see page 9-11 of response). In response to applicant's argument, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the references are all in the antibody field. In addition, Soderlind et al was cited for teaching the advantages of overlapping oligos and Yelton was cited for

providing motivation to use affinity maturation of antibodies. In addition, Yelton clearly acknowledges advances in altering the structure of antibodies to improve the therapeutic potential and cites CDR grafting as one such method for humanization which is taught by Jones (see page 2000 and reference 44). Although the claims have been amended to recite non-human donor frameworks and non-human donor CDRs and human acceptor frameworks, this limitation is in the teachings of Jones which teaches mouse CDRs and mouse frameworks as donor and human frameworks as acceptor. Thus, taken in its whole Yelton teach there is a clear advantage to have higher affinity antibodies and using these antibodies for therapy which can be humanized. The advantages of using overlapping oligos was taught by Soderlind as allowing the construction of the library in one single PCR reaction (see abstract). Thus there would be an advantage to use this technique.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

The following is a NEW GROUND of rejection

9. Claims 1-4, 6-10, 12-16, 18-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Nature 321:522, 1986) and further in view of Wu et al (PNAS 95:6037-6042, 5/98) and Soderlind et al (Gene 160:269-72, 1995) and Hagiwara et al (U.S. Patent 5,589,573, issued 12/96).

The claims recite a method of constructing a population of heavy or light chain variable region encoding nucleic acids comprising providing a non-human donor sequence and an human acceptor sequence and chemically synthesizing a population of oligos encoding for at least one modified CDR wherein at least one amino acid is different from the reference sequence and a second population of oligos encoding unmodified framework regions and mixing to create overlapping oligos and constructing the nucleic acids. Further co expressing the population with a light or heavy chain and wherein the acceptor is human and further the method comprises extending the oligos with polymerase. Further claimed is wherein the representation is in electronic form.

Jones et al teach CDR grafting of non-human CDRs into human frameworks by comparing the rodent and human sequences and producing the antibodies by synthesizing oligonucleotides and the affinity of the humanized antibody is lower than that of the parent. Jones et al does not teach a library with mutations in the CDRs and no mutations in the frameworks or construction by overlapping oligos or representation in electronic form. These deficiencies are made up for in the teachings of Wu et al, Soderlind et al and Hagiwara et al.

Wu et al teach affinity maturation of a humanized antibody by mutagenesis in the CDRs and construction of random libraries in the heavy chain and they intend to examine the light chain (see entire document).

Soderlind et al teach libraries of variable domains wherein the CDRs are mutagenized and the frameworks were unchanged and the libraries were made by overlapping oligos (see entire document).

Hagiwara et al teach amino acid sequences from a database of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Wu et al, Soderlind et al, and Hagiwara et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Wu et al, Soderlind et al, and Hagiwara et al because Jones et al teach CDR grafting onto a human framework and the antibody has a lower affinity than the murine antibody and it would be obvious to use the mutagenesis strategy of Wu et al to produce a library of CDR mutants and keep the framework residues constant because Wu et al teach antibodies which resulted in improved affinity only by altering the CDRs. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the

CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Wu et al, Soderlind et al, and Hagiwara et al because Soderlind et al teach a variable region library for an antibody produced by synthesizing overlapping oligos which resulted in construction of the library in one single PCR (see abstract) and the method resulted in a divers library in the CDRs (see page 271). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have constructed a library of heavy or light chain amino acid sequence wherein the CDRs are randomized and the framework is unmodified relative to a reference sequence and chemically synthesizing overlapping oligos and producing the heavy and light chains and providing a electronic form of the reference sequences in view of the teachings of Jones et al, Wu et al, Soderlind et al, and Hagiwara et al because Hagiwara et al teach amino acid sequences from a data base of Kabat et al and the sequences are retrievable by computer (see column 12, lines 25-40). In addition, because the database is accessible by computer it would be obvious to download the sequences onto an electronic form for storage and manipulation. Thus, it would have been obvious to produce a library wherein the CDRs are altered and the frameworks are not as taught by Wu et al and Soderlind et al and the frameworks are from a human antibody as taught by Jones et al and produce the library for screening for increased affinity and provide an electronic form of the sequences as taught by Hagiwara et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER